PCT/GB 2004 / 0 0 2 5 5 4

GB0412554

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed

Dated 21 May 2004

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Patents Form 1/77

Pa[redacted] Act 1977
(R[redacted])

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference 101113-1 GB

2. Patent application number *(The Patent Office will fill in this part)* 0314075.3

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 7822448003

If the applicant is a corporate body, give the country/state of its incorporation Sweden

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent *(if you have one)* Thomas Kerr MILLER

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4TG

Patents ADP number *(if you know it)* 7822671002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	32
Claim *(s)*	4
Abstract	1
Drawing *(s)*	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 17/06/03

12. Name and daytime telephone number of person to contact in the United Kingdom: Jennifer Bennett - 01625 230148

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

THERAPEUTIC AGENTS

Field of the invention

The present invention relates to certain novel substituted 3-phenylpropionic acid derivatives, to processes for preparing such compounds, to their the utility in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome, to methods for their therapeutic use and to pharmaceutical compositions containing them.

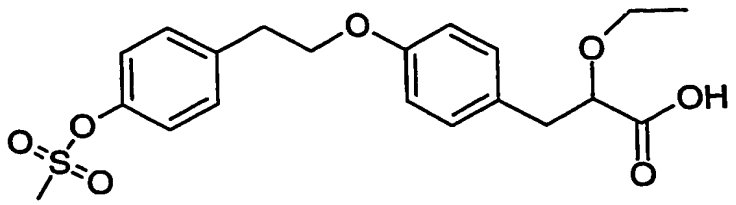
Background of the invention

The metabolic syndrome including type 2 diabetes mellitus, refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinaemia, possibly type 2 diabetes mellitus, arterial hypertension, central (visceral) obesity, dyslipidaemia observed as deranged lipoprotein levels typically characterised by elevated VLDL (very low density lipoproteins), small dense LDL particles and reduced HDL (high density lipoprotein) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In type 2 diabetes mellitus atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is awareness of the need to increase the insulin sensitivity in patients with the metabolic syndrome and thus to correct the dyslipidaemia which is considered to cause the accelerated progress of atherosclerosis. However, currently this is not a universally accepted diagnosis with well-defined pharmacotherapeutic indications.

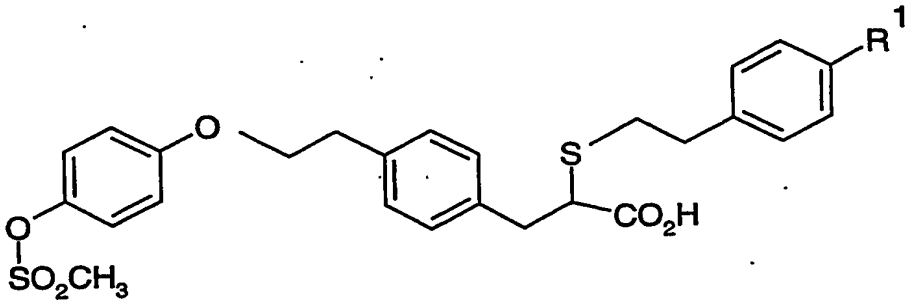
The S-enantiomer of the compound of formula C below



C

2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl]propanoic acid, is disclosed in PCT Publication Number WO99/62872. This compound is reported to be a modulator of peroxisome proliferator-activated receptors (PPAR, for a review of the PPARs see T. M.Willson et al , J Med Chem 2000, Vol 43, 527) and has combined PPARα/PPARγ agonist activity (Structure, 2001, Vol 9, 699, P. Cronet et al). This compound is effective in treating conditions associated with insulin resistance.

Co-pending PCT application No. PCT/GB02/05743 discloses compounds of formula I



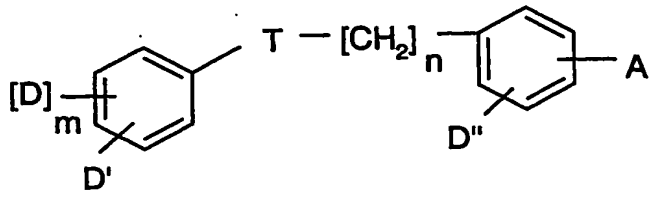
I

wherein R^1 represents chloro, fluoro or hydroxy as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof, to processes for preparing such compounds, to their the utility in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance, to methods for their therapeutic use and to pharmaceutical compositions containing them.

Surprisingly a series of compounds has now been found which are dual PPARα and PPARγ modulators.

Description of the invention

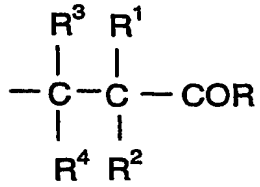
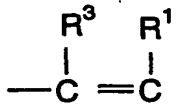
The present invention provides a compound of formula I



I

and pharmaceutically acceptable salts thereof, in which

A is situated in the ortho, meta or para position and represents

 or  , wherein

R is hydrogen;

$-OR^a$, wherein R^a represents hydrogen, alkyl, aryl or alkylaryl;

$-NR^aR^b$, wherein R^a and R^b are the same or different and R^a is as defined above and R^b represents hydrogen, alkyl, aryl, alkylaryl, cyano, - OH, -Oalkyl, -Oaryl, -Oalkylaryl, $-COR^c$ or $-SO_2R^d$, wherein R^c represents hydrogen, alkyl, aryl or alkylaryl and R^d represents alkyl, aryl or alkylaryl;

R^1 is alkyl, aryl, alkenyl, alkynyl, cyano;

$-OR^e$, wherein R^e is alkyl, acyl, aryl or alkylaryl;

$-O-[CH_2]_m-OR^f$, wherein R^f represents hydrogen, alkyl, acyl, aryl or alkylaryl and m represents an integer 1-8;

$-OCONR^aR^c$, wherein R^a and R^c are as defined above;

$-SR^d$, wherein R^d is as defined above;

$-SO_2NR^aR^f$, wherein R^f and R^a are as defined above;

$-SO_2OR^a$, wherein R^a is as defined above;

$-COOR^d$, wherein R^d is as defined above;

R^2 is hydrogen, halogen, alkyl, aryl, or alkylaryl,

R^3 and R^4 are the same or different and each represents hydrogen, alkyl, aryl, or alkylaryl,

n is an integer 1-6,

m is an integer 0 or 1 (preferably m is 1);

D is situated in the ortho, meta or para position (preferably D is situated in the para position) and represents alkyl, acyl, aryl, alkylaryl, halogen, -CN and NO_2, wherein the alkyl, aryl, or alkylaryl group is optionally substituted by R^b ;

$-NR^cCOOR^a$, wherein R^c and R^a are as defined above;

$-NR^cCOR^a$, wherein R^c and R^a are as defined above;

$-NR^cR^a$, wherein R^c and R^a are as defined above;

$-NR^cSO_2R^d$, wherein R^c and R^d are as defined above;

$-NR^cCONR^kR^c$, wherein R^a, R^c and R^k are as defined above;

$-NR^cCSNR^aR^k$, wherein R^a, R^c and R^k are as defined above;

$-OR^a$, wherein R^a is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

$-SO_2R^d$, wherein R^d is as defined above;

$-SOR^d$, wherein R^d is as defined above;

$-SR^c$, wherein R^c is as defined above;

$-SO_2NR^aR^f$, wherein R^f and R^a are as defined above;

$-SO_2OR^a$, wherein R^a is as defined above;

$-CONR^cR^a$, wherein R^c and R^a are as defined above;

$-OCONR^fR^a$, wherein R^f and R^a are as defined above;

D' is situated in the ortho, meta or para position (preferably D' is situated in the ortho or meta position) and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$, wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above;

$-OSO_2R^d$, wherein R^d is as defined above;

D'' is situated in the ortho, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$ wherein R^f and R^b are as defined above;

$-OR^f$, wherein R^f is as defined above.

$-OSO_2R^d$, wherein R^d is as defined above

and T represents O, S or NR^t wherein R^t represents alkyl or alkylaryl;

wherein the term "aryl" denotes a substituted or unsubstituted phenyl, furyl, thienyl or pyridyl group, or a fused ring system of any of these groups;
wherein the term "alkyl" denotes a straight or branched, substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms or a substituted or unsubstituted cycloalkyl having from 3 to 6 carbon atoms and wherein the term "substituted " denotes substitution by one or more alkyl, alkoxy, halogen, thiol, nitro, hydroxy, acyl, aryl or cyano groups or an amino group optionally substituted by one or two alkyl groups:

with a first proviso that when D is $CH_3S(O)_2O$ and D' is H and T is O and n=2 and A is a group $CH_2CH(SCH_2CH_2Ph)COR^x$ in which the phenyl is substituted in the 4 position by OH , Cl or F and in which R^x represents OH, or a protecting group for a carboxylic hydroxy group including a ethoxy or benzyloxy then D'' is not H.

In a particular group of compounds of formula I there is a second proviso that when m is 1 and D is $CH_3S(O)_2O$ and D' is H and T is O, S or NR and wherein R represents a H, a C_{1-6}alkyl group or a phenyl C_{1-6}alkyl group and n=2 and A is a group $CH_2CH(OC_2H_5)COR^x$ in which R^x represents OH, or a protecting group for a carboxylic hydroxy group including a C_{1-6}alkoxy group or benzyloxy then D'' is not H.

Further values of T , D and A in compounds of Formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In a first group of compounds of formula I, T is O.
In a second group of compounds of formula I, T is S.
In a third group of compounds of formula I T is NH.
In a fourth group of compounds of formula I, A is a group $CH_2CH(R^y)CO_2H$ in which R^y represents arylethyl in which the aryl is optionally substituted by one or more of the

following, C_{1-6}alkyl, C_{1-6}alkoxy, halogen, cyano or an amino group optionally substituted by one or two alkyl groups.

In a fifth group of compounds of formula I, m is 1 and D is methanesulphonyloxy.

It will be appreciated by those skilled in the art the compounds of formula I contain an optically active centre and therefore can exist as enantiomers which can be separated as described later. It is expected that most, if not all, of the activity of the compounds of formula I resides in one enantiomer: either the S or the R enantiomer or the (+) or the (–) enantiomer. The enantiomers which are more active in the assays which are described later are preferred forms of the present invention. It will be understood that the present invention includes all mixtures of this active enantiomer with the other enantiomer, for example the racemic mixture, which is a useful intermediate for the active enantiomer.

The active enantiomers may be isolated by separation of racemate for example by fractional crystallization, resolution or HPLC on a chiral column (for example a Chiralpak™ AD 250x50 column). Alternatively the active enatiomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation with a chiral reagent.

The following definitions shall apply throughout the specification and the appended claims with regard to the group A.

Unless otherwise stated or indicated, the term "alkyl" denotes a straight or branched, substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms or a cyclic alkyl having from 3 to 6 carbon atoms. The term "lower alkyl" denotes a straight or branched, substituted or unsubstituted alkyl group having from 1 to 3 carbon atoms or a cyclic alkyl having 3 carbon atoms. Examples of said alkyl and lower alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl as well as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

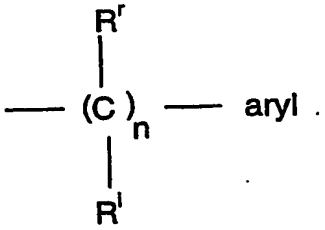
Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

Unless otherwise stated or indicated, the term "aryl" denotes a substituted or unsubstituted phenyl, furyl, thienyl or pyridyl group, or a fused ring system of any of these groups, such as naphthyl.

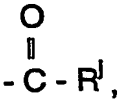
Unless otherwise stated or indicated, the term "substituted " denotes an alkyl or an aryl group as defined above which is substituted by one or more alkyl, alkoxy, halogen, amino, thiol, nitro, hydroxy, acyl, aryl or cyano groups.

Unless otherwise stated or indicated, the term "alkylaryl" denotes a



wherein n is an integer 1 to 6 and R^r and R^i are the same or different and each represents hydrogen or an alkyl or aryl group as defined above.

Unless otherwise stated or indicated, the term "acyl" denotes a group



wherein R^j is hydrogen, alkyl, alkoxy, aryl and alkylaryl as defined above.

Unless otherwise stated or indicated, the terms "alkenyl" and "alkynyl" denote a straight or branched, substituted or unsubstituted unsaturated hydrocarbon group having one or more double or triple bonds and having a maximum of 6 carbon atoms, preferably 3 carbon atoms.

Unless otherwise stated or indicated the term "protective group" (R^P) denotes a protecting group as described in the standard text "Protecting groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts. The protective group may also be a polymer resin such as Wang resin or 2-chlorotrityl chloride resin.

For the groups other than A the following definitions apply.
"Cycloalkyl" means a non-aromatic monocyclic or multicyclic ring system of from 3 carbon atoms up to 10 carbon atoms.

"Aryl" means an aromatic monocyclic or multicyclic ring system of up to 14 carbon atoms.

"Heterocyclyl" means a non-aromatic monocyclic or multicyclic ring system of up to 14 carbon atoms, containing at least one heteroatom .

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system of up to 14 carbon atoms, containing at least one heteroatom.

The term "prodrug " as used in this specification includes derivatives of the carboxylic acid group which are converted in a mammal, particularly a human, into the carboxylic acid group or a salt or conjugate thereof. The term "prodrug " also includes derivatives of the hydroxy substituent (when R^1 represents hydroxy) which are converted in a mammal, particularly a human, into the hydroxy group or a salt or conjugate thereof. It should be understood that, whilst not being bound by theory, it is believed that most of the activity associated with the prodrugs arises from the activity of the compound of formula I into

which the prodrugs are converted. Prodrugs can be prepared by routine methodology well within the capabilities of someone skilled in the art. Various prodrugs of carboxy and hydroxy are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology. 42: 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p.113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8:1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77:285 (1988); and

e) N. Kakeya, *et al.*, Chem Pharm Bull, 32:692 (1984).

The above documents a to e are herein incorporated by reference.

In vivo cleavable esters are just one type of prodrug of the parent molecule. An *in vivo* hydrolysable (or cleavable) ester of a compound of the formula (I) that contains a carboxy or a hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters, for example, methoxymethyl; C_{1-6}alkanoyloxymethyl esters, for example, pivaloyloxymethyl; phthalidyl esters; C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters, for example, 1-cyclohexyl-carbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example, 5-methyl-1,3-dioxolen-2-onlymethyl; and C_{1-6}alkoxycarbonyloxyethyl esters, for example, 1-methoxycarbonyloxyethyl; and may be formed at any carboxy group in the compounds of this invention. An *in vivo* hydrolysable (or cleavable) ester of a compound of the formula (I) that contains a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino

linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

The compounds of formula I have activity as medicaments, in particular the compounds of formula I are agonists of PPARα and PPARγ.

Specific compounds of the invention are one or more of the following:
2-[(4-Cyanobenzyl)thio]-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid
2-({2-[4-(Dimethylamino)phenyl]ethyl}thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid
3-[4-(2-{4-[(Methylsulfonyl)oxy]phenoxy}ethyl)phenyl]-2-{[2-(2-thienyl)ethyl]thio}-propanoic acid
2-{[2-(2-Fluorophenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]-propanoic acid and
2-{[2-(3-Methoxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid
and pharmaceutically acceptable salts thereof.

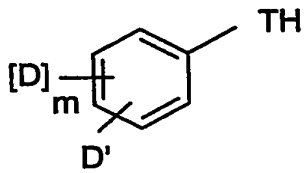
It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms. Certain compounds of the present invention may exist as tautomers. It is to be understood that the present invention encompasses all such tautomers.

Methods of preparation

The compounds of the invention may be prepared as described in the Examples and analogous methods thereto known to persons skilled in the art. In particular methods disclosed in WO 99/62871 and analogous methods thereto may be used. However, the invention is not limited to these methods, the compounds may also be prepared as

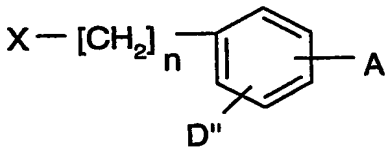
described for structurally related compounds in the prior art. The reactions can be carried out according to standard procedures or as described in the experimental section.

Compounds of formula I may be prepared by reacting a compound of formula II



II

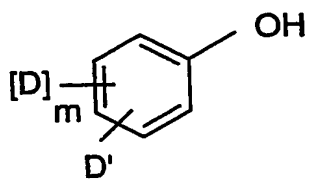
in which D, m, D' and T are as previously defined with a compound of formula III



III

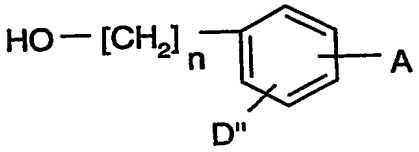
in which n, A and D" are as previously defined and X is a leaving group for example halo or methanesulphonyloxy at a temperature in the range of 0-150°C optionally on the presence of an inert sovent. Optionally protection and deprotection steps known to those skilled in the art may be used as as necessary.

Compounds of formula I in which T is O may be prepared by reacting a compound of formula IV



IV

in which D, m and D' are as previously defined with a compound of formula V



V

in which n, A and D" are as previously defined using Mitsonobu conditions known to those skilled in the art for example in the presence of a coupling agent, for example cyanomethylenetri-N-butylphosphorane.

Compounds of formula II, III, IV, and V may be prepared by methods known to those skilled in the art see for example WO 99/62871 herein incorporated by reference.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free acid, or a pharmaceutical acceptable organic or inorganic base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in therapeutical treatment of humans are about 0.0001-100 mg/kg body weight, preferably 0.001-10 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The present compounds of formula (I) are useful for the prophylaxis and/or treatment of clinical conditions associated with inherent or induced reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders (also known as metabolic syndrome). These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia, type 2 diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoprotein (VLDL) triglyceride rich particles, high Apo B levels, low high density lipoprotein (HDL) levels associated with low apoAI particle levels and high Apo B levels in the presence of small, dense, low density lipoproteins (LDL) particles, phenotype B.

The compounds of the present invention are expected to be useful in treating patients with combined or mixed hyperlipidemias or various degrees of hypertriglyceridemias and postprandial dyslipidemia with or without other manifestations of the metabolic syndrome.

Treatment with the present compounds is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macro-angiopathies of various internal organs causing myocardial infarction, congestive heart failure, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of their insulin sensitizing effect the compounds of formula I are also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term complications associated with chronic hyperglycaemia in diabetes mellitus such as the micro-angiopathies causing renal disease, retinal damage and peripheral vascular disease of the lower limbs are expected to be delayed. Furthermore the compounds may be useful in treatment of various conditions outside the cardiovascular system whether or not associated with insulin resistance, like polycystic ovarian syndrome, obesity, cancer and

states of inflammatory disease including neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease, Parkinson's disease and multiple sclerosis.

The compounds of the present invention are expected to be useful in controlling glucose levels in patients suffering from type 2 diabetes.

The present invention provides a method of treating or preventing dyslipidemias, the insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the administration of a compound of formula I to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating or preventing type 2 diabetes comprising the administration of an effective amount of a compound of formula I to a mammal (particularly a human) in need thereof.

In a further aspect the present invention provides the use of a compound of formula I as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the manufacture of a medicament for the treatment of insulin resistance and/or metabolic disorders.

Combination Therapy

The compounds of the invention may be combined with other therapeutic agents that are useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, for example metformin, phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors). An example of an alpha-glucosidase inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is repaglinide or nateglinide.

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with another PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to NN622/Ragaglitazar, BMS 298585, WY-14643, clofibrate, fenofibrate, bezafibrate, gemfibrozil and ciprofibrate; GW 9578, ciglitazone, troglitazone, pioglitazone, rosiglitazone, eglitazone, proglitazone, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)-phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

In addition the combination of the invention may be used in conjunction with a sulfonylurea for example: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chloropropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide,

phenbutamide, tolcylamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. Therefore the present invention includes administration of a compound of the present invention in conjunction with one, two or more existing therapies described in this paragraph. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA. Alternatively smaller doses may be used as a result of the benefits derived from the combination.

The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, bervastatin, cerivastatin, dalvastatin, fluvastatin, itavastatin, lovastatin, mevastatin, nicostatin, nivastatin, pravastatin and simvastatin, or a pharmaceutically acceptable salt, especially sodium or calcium, or a solvate thereof, or a solvate of such a salt. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A particularly preferred statin is, however, a compound with the chemical name (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[*N*-methyl-*N*-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt. The compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl-(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts are disclosed in European Patent Application, Publication No. EP-A-0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444. This latter statin is now known under its generic name rosuvastatin.

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor).

Suitable compounds possessing IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818, WO 98/38182, WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051, EP 864 582, EP489423, EP549967, EP573848, EP624593, EP624594, EP624595 and EP624596 and the contents of these patent applications are incorporated herein by reference.

Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiepines, and the compounds described in the claims, particularly claim 1, of WO 00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl β-D-glucopyranosiduronic acid (EP 864 582). Other suitable IBAT inhibitors include one of:

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a

salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;

a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;

a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;

a nicotinic acid derivative, including slow release and combination products, for example, nicotinic acid (niacin), acipimox and niceritrol;

a phytosterol compound for example stanols;

probucol;

an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist for example as described in WO01/70700 and EP 65635 ;

a Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in combination

with a compound of formula I include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of formula I include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;

b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Examples

^{1}H NMR and ^{13}C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at ^{1}H frequencies of 300, 400, 500 and 600 MHz, respectively, and at ^{13}C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale (δ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Abbreviations

DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
DMF	*N,N*-dimethylformamide
THF	tetrahydrofuran
MeCN	acetonitrile
MeOH	methanol
TFA	trifluoroacetic acid
NH_4OAc	ammonium acetate
t	triplet
s	singlet
d	doublet
q	quartet
m	multiplet
bs	broad singlet

Starting Materials and Intermediates

Compound A. *S*-(4-Cyanobenzyl) ethanethioate

To a stirred solution of 4-(bromomethyl)benzonitrile (4.00 mmol, 784 mg) and thioacetic acid (4.20 mmol, 320 mg) in MeOH (8 mL) was added dropwise triethylamine (4.20 mmol, 425 mg). After cooling, the resulting solution was used in the next reaction step.

Compound B. *S*-{2-[4-(Dimethylamino)phenyl]ethyl} ethanethioate

2-[4-(Dimethylamino)phenyl]ethanol (4.00 mmol, 661 mg) and triethylamine (4.80 mmol, 486 mg) were dissolved in DCM (15 mL) and cooled in an ice-bath. Methanesulfonyl chloride (4.40 mmol, 504 mg) was added in portions and the ice-bath was removed. After 1.5 h water was added. The phases were separated. The organic phase was filtered through $MgSO_4$ and evaporated to dryness. The crude mesylate was dissolved in MeOH (8 mL). To this solution was added triethylamine (4.20 mmol, 425 mg) and thioacetic acid (4.20 mmol, 320 mg). After cooling, the resulting solution was used in the next reaction step.

Compound C. *S*-[2-(2-Thienyl)ethyl] ethanethioate

A solution of the title compound was prepared from 2-(2-thienyl)ethyl methanesulfonate using the procedure described for compound A.

Compound D. *S*-[2-(2-fluorophenyl)ethyl] ethanethioate

A solution of the title compound was prepared from 2-(2-fluorophenyl)ethanol using the procedure described for compound B.

Compound E. *S*-[2-(3-Methoxyphenyl)ethyl] ethanethioate

A solution of the title compound was prepared from 2-(3-methoxyphenyl)ethanol using the procedure described for compound B.

Compound F.
Methyl 2-chloro-3-[4-(2-{4-[(methylsufonyl)oxy]phenoxy}ethyl)phenyl]propanoate

(i) Methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate

2-(4-Aminophenyl)ethanol (11g, 81mmol) and 32ml conc HCl was dissolved in acetone and cooled to 0°C. Sodium nitrite (5.6g, 81mmol) in 20ml water was added dropwise. The temperature was kept under 0°C. After one hour, methyl acrylate (70g, 808mmol) and CuI (1.6g, 8mmol) were added (<0°C). The reaction mixture was stirred at room temperature overnight.

The solvent was evaporated and water was added. The water phase was extracted three times with EtOAc, the organic phases were pooled and washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash chromatography using a 65:35 mixture of EtOAc and heptane as eluent. Further purification by preparative HPLC (using a gradient of CH_3CN/ 5%CH_3CN-waterphase containing 0.1M NH_4OAc as eluent) gave 9.7g product (yield 49%) as an oil.

^{1}HNMR (400MHz, $CDCl_3$): 2.84 (t, 3H), 3.15 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 3.84 (t, 3H), 4.43 (t, 1H), 7.17 (d, 4H)

(ii) Methyl 3-(4-{2-[4-(benzyloxy)phenoxy]ethyl}phenyl)-2-chloropropanoate

Triphenylphosphine (2.4g, 9mmol) was added to a solution of methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate (2.1g, 8.5mmol) and 4-(benzyloxy)phenol (1.7g, 8mmol) in 20ml toluene under nitrogen atmosphere. The solution was warmed to 55°C and diisopropyl azodicarboxylate (1.8g, 9mmol) was added. The reaction mixture was stirred at 55°C overnight.

The mixture was allowed to cool and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography using a 80:20 mixture of heptane and EtOAc as eluent to yield 2.28g of the desired product (yield 61%) as colourless crystals.

^{1}HNMR (400MHz, $CDCl_3$): 3.05 (t, 2H), 3.16 (dd, 1H), 3.36 (dd, 1H), 3.75 (s, 3H), 4.12 (t, 2H), 4.45 (t, 1H), 5.01 (s, 2H), 6.82 (m, 2H), 6.90 (m, 2H), 7.13-7.27 (m, 4H), 7.29-7.47 (m, 5H).

(iii) Methyl 2-chloro-3-{4-[2-(4-hydroxyphenoxy)ethyl]phenyl}propanoate

Methyl 3-(4-{2-[4-(benzyloxy)phenoxy]ethyl}phenyl)-2-chloropropanoate (1.0g, 2.4mmol) and dimethyl sulfide (0.9g, 14mmol) was dissolved in 60ml CH_2Cl_2. Boron trifluoride etherate (2.0g, 14mmol) was added droppwise to the stirred solution. The reaction mixture was stirred for two days at room temperature. Another equivalent (0.4g, 2.87mmol) boron trifluoride etherate was added and the stirring was continued overnight. Water was added. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The organic phases were pooled, washed (water, brine), dried (Na_2SO_4) and evaporated under reduced pressure. Futher purification by preparative HPLC using a gradient of CH_3CN/ 5% CH_3CN-waterphase containing 0.1M NH_4OAc gave 0.55g of the desired product (yield 52%) as an oil.
^{1}HNMR (400MHz, $CDCl_3$): 3.04 (t, 2H), 3.16 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 4.10 (t, 2H), 4.40 (t, 1H), 6.75 (m, 4H), 7.12-7.29 (m, 4H).

(iv) Methyl 2-chloro-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate

Methyl 2-chloro-3-{4-[2-(4-hydroxyphenoxy)ethyl]phenyl}propanoate (334mg, 1.0mmol) and triethylamine (303mg, 3.0mmol) was dissolved in 20ml dichloromethane and cooled to -20°C under nitrogen atmosphere. Methanesulfonyl chloride (114mg, 1.0mmol) was added dropwise. The mixture was allowed to reach room temperature. After 2 hours dichlormethane was added, the mixture was washed (water, brine), dried (Na_2SO_4) and evaporated under reduced pressure to yield 394mg pure product (yield 96%).
^{1}HNMR (400MHz, $CDCl_3$): 3.02-3.11 (m,5H), 3.15 (dd, 1H), 3.35 (dd,1H), 3.74 (s, 3H), 4.14 (t, 2H), 4.44 (t, 1H), 5.29 (s, 2H), 6.88 (d, 2H), 7.14-7.25 (m, 6H).

Examples

Example 1
2-[(4-Cyanobenzyl)thio]-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid

The reaction was performed under an argon atmosphere. To 0.80 mL of a stirred solution of compound A (0.40 mmol) in MeOH was added sodium methane thiolate (0.80 mmol, 56

mg) in MeOH (0.20 mL). After one hour of stirring, compound F (0.48 mmol, 200 mg) in MeCN was added. After 16 h of stirring, the mixture was evaporated to dryness using a vacuum centrifuge. The remaining crude product was dissolved in 0.5 M LiOH solution (THF/water 7:1, 0.50 mL) and stirred for 20 hours. After acidification with 12 M HCl (100 μL) the stirring was continued for one hour. The crude product was filtered through a Teflon™ filter and purified using preparative HPLC (C8-column, gradient of 0.2 % TFA/MeCN) to give 24 mg of the title compound. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.80-2.88 (m, 1H), 3.06 (t, J=6.9 Hz, 2H), 3.10 (s, 3H), 3.10-3.18 (m, 1H), 3.30 (t, J=7.7 Hz, 1H), 3.77-3.93 (m, 2H), 4.15 (t, J=6.9 Hz, 2H), 6.85-6.90 (m, 2H), 7.00-7.06 (m, 2H), 7.14-7.20 (m, 4H), 7.33-7.38 (m, 2H), 7.50-7.55 (m, 2H)

Example 2

2-({2-[4-(Dimethylamino)phenyl]ethyl}thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid

The title compound (yield 6 mg) was prepared from compound B and F using the procedure described for example 1. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.70-2.96 (m, 5H), 2.90 (s, 6H), 3.05 (t, J=7.0 Hz, 2H), 3.10 (s, 3H), 3.13-3.20 (m, 2H), 3.47-3.53 (m, 2H), 4.12 (t, J=7.0 Hz, 2H), 6.66-6.72 (m, 2H), 6.83-6.89 (m, 2H), 7.00-7.05 (m, 2H), 7.13-7.20 (m, 4H)

Example 3

3-[4-(2-{4-[(Methylsulfonyl)oxy]phenoxy}ethyl)phenyl]-2-{[2-(2-thienyl)ethyl]thio}propanoic acid

The title compound (yield 3 mg) was prepared from compound C and F using the procedure described for example 1. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.85-3.00 (m, 4H), 3.02-3.13 (m, 6H), 3.15-3.22 (m, 1H), 3.50-3.56 (m, 1H), 4.13 (t, J=7.0 Hz, 2H), 6.77-6.80 (m, 1H), 6.84-6.87 (m, 2H), 6.87-6.92 (m, 1H), 7.10-7.13 (m, 1H), 7.15-7.19 (m, 6 H)

Example 4

2-{[2-(2-Fluorophenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid

The title compound (yield 2 mg) was prepared from compound D and F using the procedure described for example 1. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.83-2.94 (m, 4H), 2.94-3.00 (m, 1H), 3.05 (t, J=7.1 Hz, 2H), 3.09 (s, 3H), 3.14-3.22 (m, 1H), 3.51-3.57 (m, 1H), 4.13 (t, J=7.1 Hz, 2H), 6.83-6.88 (m, 2H), 6.96-7.02 (m, 1H), 7.03-7.06 (m ,1H), 7.11-7.22 (m, 8 H)

Example 5

2-{[2-(3-Methoxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid

The title compound (yield 16 mg) was prepared from compound E and F using the procedure described for example 1. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.99-2.19 (m, 5H), 2.30 (t, J=6.9 Hz, 2H), 2.34 (s, 3H), 2.35-2.41 (m, 1H), 2.69-2.75 (m, 1H), 3.00 (s, 3H), 3.37 (t, J=6.9 Hz), 5.92-6.04 (m, 6 H), 6.37-6.48 (m, 4H), 6.52-6.58 (m, 2H)

Biological activity

Formulations

Compounds were dissolved in DMSO to obtain 16 mM stock solutions. Before assays, stock solutions were further diluted in DMSO and culture media.

GENERAL CHEMICALS AND REAGENTS

Luciferase assay reagent was purchased from Packard, USA. Restriction Enzymes were from Boehringer and Vent polymerase from New England Biolabs.

CELL LINES AND CELL CULTURE CONDITIONS

U2-OS, (Osteogenic sarcoma, Human) was purchased from ATCC, USA. Cells were expanded and refrozen in batches from passage number six. Cells were cultured in Dulbecco's modified Eagle medium (DMEM) with 25 mM glucose, 2 mM glutamine or 4

mM L-alanyl-L-glutamine,10% fetal calf serum, at 5% CO_2. Phosphate buffered saline (PBS) without addition of calcium or magnesium was used. All cell culture reagents were from Gibco (USA) and 96-well cell culture plates were purchased from Wallach.

PLASMID CONSTRUCTS FOR HETEROLOGOUS EXPRESSION

Standard recombinant DNA techniques were carried out as described by Ausubel (7). The Luciferase reporter vector, pGL5UAS (clone consists of five copies of the GAL4 DNA binding sequence, 5′-CGACGGAGTACTGTCCTCCGAGCT-3′, cloned into the SacI/XhoI sites of pGL3-Promoter (Promega). The SacI/XhoI fragment carrying the UAS sites was constructed using annealed overlapping oligonucleotides.

Expression vectors used are based upon pSG5 (Stratagene). All vectors contain an EcoRI/NheI fragment encoding the DNA binding domain of GAL4 (encoding amino acid positions 1-145 of database accession number P04386) followed by an in-frame fusion to a fragment encoding the nuclear localisation sequence from T antigen of Polyoma Virus. The nuclear localisation sequence was constructed using annealed overlapping oligonucleotides creating NheI/KpnI sticky ends (5′-CTAGCGCTCCTAGAAGAAACGCAAGGTTGGTAC-3'). The ligand binding domains from human and mouse PPARα and human and mouse PPARγ were PCR amplified as KpnI/BamHI fragments and cloned in frame to the GAL4 DNA binding domain and the nuclear localisation sequence. The sequence of all plasmid constructs used were confirmed by sequencing.

The following expression vectors were used for transient transfections:

vector	encoded PPAR subtype	sequence reference[1]
pSGGALhPPa	human PPARα	S74349, nt 625-1530
pSGGALmPPa	murine PPARα	X57638, nt 668-1573
pSGGALhPPg	human PPARγ	U63415, nt 613-1518
pSGGALmPPg	murine PPARγ	U09138, nt 652-1577

[1] refers to nucleotide positions of data base entry used to express the ligand binding domain.

TRANSIENT TRANSFECTIONS

Frozen stocks of cells from passage number six were thawed and expanded to passage number eight before transfections. Confluent cells were trypsinised, washed and pelleted by centrifugation at 270xg for 2 minutes. The cell pellet was resuspended in cold PBS to a cell concentration of about 18 x 10^6 cells/ml. After addition of DNA, the cell suspension was incubated on ice for approximately 5 minutes before electroporation at 230 V, 960 μF in Biorad's Gene Pulser™ in 0.5 ml batches. A total of 50 μg DNA was added to each batch of 0.5 ml cells, including 2.5 μg expression vector, 25 μg reporter vector and 22.5 μg unspecific DNA (pBluescript, Stratagene).

After electroporation, cells were diluted to a concentration of 320'000 cells/ml in DMEM without phenol red, and approximately 25'000 cells/well were seeded in 96-well plates. In order to allow cells to recover, seeded plates were incubated at 37°C for 3-4 hours before addition of test compounds. In assays for PPARα, the cell medium was supplemented with resin-charcoal stripped fetal calf serum (FCS) in order to avoid background activation by fatty acid components of the FCS. The resin-charcoal stripped FCS was produced as follows; for 500 ml of heat-inactivated FCS, 10 g charcoal and 25 g Bio-Rad Analytical Grade Anion Exchange Resin 200-400 mesh were added, and the solution was kept on a

magnetic stirrer at room temperature over night. The following day, the FCS was centrifuged and the stripping procedure was repeated for 4-6 hours. After the second treatment, the FCS was centrifuged and filter sterilised in order to remove remnants of charcoal and resin.

ASSAY PROCEDURE

Stock solutions of compounds in DMSO were diluted in appropriate concentration ranges in master plates. From master plates, compounds were diluted in culture media to obtain test compound solutions for final doses.

After adjustment of the amount of cell medium to 75 µl in each well, 50 µl test compound solution was added. Transiently transfected cells were exposed to compounds for about 24 hours before the luciferase detection assay was performed. For luciferase assays, 100 µl of assay reagent was added manually to each well and plates were left for approximately 20 minutes in order to allow lysis of the cells. After lysis, luciferase activity was measured in a 1420 Multiwell counter, Victor, from Wallach.

Reference compounds

The TZD pioglitazone was used as reference substance for activation of both human and murine PPARγ. 5,8,11,14-Eicosatetrayonic acid (ETYA) was used as reference substance for human PPARα.

Calculations and analysis

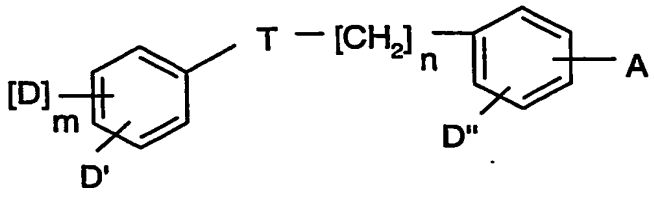
For calculation of EC_{50} values, a concentration-effect curve was established. Values used were derived from the average of two or three independent measurements (after subtraction of the background average value) and were expressed as the percentage of the maximal activation obtained by the reference compound. Values were plotted against the logarithm of the test compound concentration. EC_{50} values were estimated by linear intercalation

between the data points and calculating the concentration required to achieve 50% of the maximal activation obtained by the reference compound.

The compounds of formula I have an affinity for PPARα and PPARγ.

CLAIMS

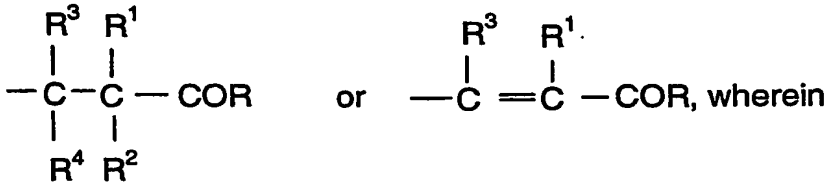
1. A compound of formula I



I

and pharmaceutically acceptable salts thereof, in which

A is situated in the ortho, meta or para position and represents



R is hydrogen;

$-OR^a$, wherein R^a represents hydrogen, alkyl, aryl or alkylaryl;

$-NR^aR^b$, wherein R^a and R^b are the same or different and R^a is as defined above and R^b represents hydrogen, alkyl, aryl, alkylaryl, cyano, - OH, -Oalkyl, -Oaryl, -Oalkylaryl, $-COR^c$ or $-SO_2R^d$, wherein R^c represents hydrogen, alkyl, aryl or alkylaryl and R^d represents alkyl, aryl or alkylaryl;

R^1 is alkyl, aryl, alkenyl, alkynyl, cyano;

$-OR^e$, wherein R^e is alkyl, acyl, aryl or alkylaryl;

$-O-[CH_2]_m-OR^f$, wherein R^f represents hydrogen, alkyl, acyl, aryl or alkylaryl and m represents an integer 1-8;

$-OCONR^aR^c$, wherein R^a and R^c are as defined above;

$-SR^d$, wherein R^d is as defined above;

$-SO_2NR^aR^f$, wherein R^f and R^a are as defined above;

$-SO_2OR^a$, wherein R^a is as defined above;

$-COOR^d$, wherein R^d is as defined above;

R^2 is hydrogen, halogen, alkyl, aryl, or alkylaryl,
R^3 and R^4 are the same or different and each represents hydrogen, alkyl, aryl, or alkylaryl,
n is an integer 1-6,
m is an integer 0 or 1 (preferably m is 1);
D is situated in the ortho, meta or para position (preferably D is situated in the para position) and represents alkyl, acyl, aryl, alkylaryl, halogen, -CN and NO_2, wherein the alkyl, aryl, or alkylaryl group is optionally substituted by R^b;
$-NR^cCOOR^a$, wherein R^c and R^a are as defined above;
$-NR^cCOR^a$, wherein R^c and R^a are as defined above;
$-NR^cR^a$, wherein R^c and R^a are as defined above;
$-NR^cSO_2R^d$, wherein R^c and R^d are as defined above;
$-NR^cCONR^kR^c$, wherein R^a, R^c and R^k are as defined above;
$-NR^cCSNR^aR^k$, wherein R^a, R^c and R^k are as defined above;
$-OR^a$, wherein R^a is as defined above;
$-OSO_2R^d$, wherein R^d is as defined above;
$-SO_2R^d$, wherein R^d is as defined above;
$-SOR^d$, wherein R^d is as defined above;
$-SR^c$, wherein R^c is as defined above;
$-SO_2NR^aR^f$, wherein R^f and R^a are as defined above;
$-SO_2OR^a$, wherein R^a is as defined above;
$-CONR^cR^a$, wherein R^c and R^a are as defined above;
$-OCONR^fR^a$, wherein R^f and R^a are as defined above;
D' is situated in the ortho, meta or para position (preferably D' is situated in the ortho or meta position) and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$,
$-NR^fR^b$, wherein R^f and R^b are as defined above;
$-OR^f$, wherein R^f is as defined above;
$-OSO_2R^d$, wherein R^d is as defined above;

D'' is situated in the ortho, meta or para position and represents hydrogen, alkyl, acyl, aryl, alkylaryl, halogen, -CN, $-NO_2$, $-NR^fR^b$ wherein R^f and R^b are as defined above;
$-OR^f$, wherein R^f is as defined above.

$-OSO_2R^d$, wherein R^d is as defined above

and T represents O, S or NR^t wherein R^t represents alkyl or alkylaryl;

wherein the term "aryl" denotes a substituted or unsubstituted phenyl, furyl, thienyl or pyridyl group, or a fused ring system of any of these groups;
wherein the term "alkyl" denotes a straight or branched, substituted or unsubstituted alkyl group having from 1 to 6 carbon atoms or a substituted or unsubstituted cycloalkyl having from 3 to 6 carbon atoms and wherein the term "substituted " denotes substitution by one or more alkyl, alkoxy, halogen, thiol, nitro, hydroxy, acyl, aryl or cyano groups or an amino group optionally substituted by one or two alkyl groups:

with a first proviso that when D is $CH_3S(O)_2O$ and D' is H and T is O and n=2 and A is a group $CH_2CH(SCH_2CH_2Ph)COR^x$ in which the phenyl is substituted in the 4 position by OH , Cl or F and in which R^x represents OH, or a protecting group for a carboxylic hydroxy group including a ethoxy or benzyloxy then D'' is not H.

2. A compound selected from
one or more of the following:
2-[(4-Cyanobenzyl)thio]-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid
2-({2-[4-(Dimethylamino)phenyl]ethyl}thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid
3-[4-(2-{4-[(Methylsulfonyl)oxy]phenoxy}ethyl)phenyl]-2-{[2-(2-thienyl)ethyl]thio}-propanoic acid
2-{[2-(2-Fluorophenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]-propanoic acid and
2-{[2-(3-Methoxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid
and pharmaceutically acceptable salts thereof.

3. A pharmaceutical formulation comprising a compound according to either claim 1 or claim 2 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

4. A pharmaceutical formulation comprising a compound according to either claim 1 or claim 2 in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

5. A method of treating or preventing lipid disorders (dyslipidemia) whether or not associated with insulin resistance comprising the administration of a compound according either claim 1 or claim 2 to a mammal in need thereof.

6. The use of a compound according either claim 1 or claim 2 in the manufacture of a medicament for the treatment of lipid disorders (dyslipidemia) whether or not associated with insulin resistance.

7. A method of treating or preventing type 2 diabetes comprising the administration of an effective amount of a compound of formula I according to either claim 1 or claim 2 to a mammal in need thereof.

8. A pharmaceutical composition comprising a compound as claimed in either claim 1 or claim 2 combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity.

ABSTRACT

Substituted 3-phenylpropionic acid derivatives, processes for preparing such compounds, their the utility in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance, methods for their therapeutic use and pharmaceutical compositions containing them.